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(54) Title: A METHOD FOR PREVENTING URTICARIA

(57) Abstract: The present invention relates to the use of a compound selected from efletirizine, cetirizine or an individual optical isomer of cetirizine or a pharmaceutically acceptable salt of any of these for the preparation of a medicament intended for preventing, or delaying the onset of, an urticaria attack in a patient.

A Method for Preventing Urticaria

The present invention relates to a method for preventing, or delaying the onset of urticaria attack with a compound selected from efletirizine, cetirizine, or an individual optical isomer of cetirizine or a pharmaceutically acceptable salt of any of these.

The present invention relates to a method for preventing, or delaying the onset of primary urticaria with a compound selected from efletirizine, cetirizine or an individual optical isomer of cetirizine or a pharmaceutically acceptable salt of any of these.

Urticaria is an inflammatory disease characterized by erythematous, itchy edematous and whealing lesions of the skin or mucous membranes. Individual wheals may be as small as 1-2 mm in diameter, but they can reach several centimeters. Acute urticaria has been defined as episodes lasting for less than 12 weeks particularly 6-12 weeks, chronic urticaria has been defined as episodes lasting beyond 12 weeks.

Different types of urticaria are described such as, but not limited to, acute idiopathic, chronic idiopathic, IgE-mediated , pseudo-allergic, serum-sickness, contact, hereditary angioedema, acquired C1 inhibitor deficiency and physical as well as urticaria vasculitis.

The onset of urticaria attack can be defined as a new flare up of urticaria in a patient, who had already experienced urticaria. Rash or flare up means that an urticaria lesion is already present. The onset of primary urticaria can be defined as the first urticaria attack during a patient's life or an attack at a time when the patient did not otherwise show any presence of urticaria; in this latter case, no urticaria lesions are present at the time of onset.

The term "cetirizine" as used herein refers to 2-[2-[4-(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]acetic acid.

The term "individual optical isomer of cetirizine" as used herein refers to the levorotatory and the dextrorotatary enantiomers of cetirizine. More precisely, it refers to the active substance comprising at least 90% by weight, preferably at least 95% by weight, of one individual optical isomer of cetirizine and at most 10% by weight, preferably at most 5% by weight, of the other individual optical isomer of cetirizine. The dextrorotatory enantiomer of cetirizine is also known as levocetirizine and in the form of its dihydrochloride salt is levorotatory. Each individual optical isomer may be obtained by conventional means, i.e., resolution from the corresponding racemic mixture or by asymmetric synthesis.

Processes for preparing cetirizine, an individual optical isomer thereof or a pharmaceutically acceptable salt thereof have been described in European Patent No. EP 0 058 146 B1, Great Britain Patents Nos. 2.225.320 and 2.225.321, United States

Patent No. 5,478,941, published European Patent Application Nos. EP 0 601 028 A1 and EP 0 801 064 A1 and published International Patent Application No. WO 97/37982.

The term "efletirizine" as used herein refers to 2-[2-[4-[bis(4-fluorophenyl)methyl]-1-piperazinyl]ethoxy]acetic acid.

Two pseudopolymorphic crystalline forms of efletirizine dihydrochloride, namely anhydrous efletirizine dihydrochloride and efletirizine dihydrochloride monohydrate are described in the European patent No. 1 034 171.

Processes for preparing efletirizine or a pharmaceutically acceptable salt thereof have been described in European Patent 1 034 171, and in the international patent application WO 97/37982.

Unless otherwise mentioned, the invention concerns all forms of efletirizine and cetirizine and pharmaceutically acceptable salts thereof.

Antihistamines are also known for the symptomatic treatment of urticaria and other skin disorders in which histamine plays a role (J. Allergy Clin. Immunol., 1995, 95,759-64).

However, there remains a need for therapeutic methods and pharmaceutical compositions which prevent, or delay the onset of, urticaria attack and/or primary urticaria particularly in infants and/or young children, one of the major groups at risk of developing the disease, because of the relative immaturity of their immune systems and their physiological barriers to allergens.

A first purpose of the invention therefore concerns the primary prevention of primary urticaria.

A second purpose of the invention is the prevention of urticaria attacks in high risk patients, such as patients who have already suffered from urticaria attacks.

A third purpose of the invention is the prevention of primary urticaria in children and particularly in atopic children or children with a direct relative family history of atopy.

A fourth purpose of the invention is the prevention of urticaria attacks in children suffering from atopic dermatitis and/or with a direct relative family history of atopy.

A fifth purpose of the invention is the prevention of acute urticaria attacks.

The present invention is based on the unexpected finding that administration of efletirizine, cetirizine or an individual optical isomer of cetirizine or a pharmaceutically acceptable salt of any of these prevents urticaria attacks especially in infants.

The present invention therefore concerns the use of a compound selected from efletirizine, cetirizine or an individual optical isomer of cetirizine or a pharmaceutically

acceptable salt of any of these for the preparation of a medicament intended for preventing, or delaying the onset of, an urticaria attack in a patient.

The present invention further concerns the use of a compound selected from efletirizine, cetirizine or an individual optical isomer of cetirizine or a pharmaceutically acceptable salt of any of these for the preparation of a medicament intended for preventing, or delaying the onset of, primary urticaria in a patient, the said medicament being administered to the patient prophylactically prior to the onset of the urticaria .

The present invention further concerns the use of a compound selected from efletirizine, cetirizine or an individual optical isomer of cetirizine or a pharmaceutically acceptable salt of any of these for the preparation of a medicament intended for preventing, or delaying the onset of, acute urticaria in a patient.

The present invention further concerns the use of a compound selected from efletirizine, cetirizine or an individual optical isomer of cetirizine or a pharmaceutically acceptable salt of any of these for the preparation of a medicament intended for preventing, or delaying the occurrence or re-occurrence of urticaria in a patient.

In addition the present invention concerns a method for preventing or delaying the onset of urticaria attack which comprises administering to a patient a therapeutically effective amount of a compound selected from efletirizine, cetirizine or an individual optical isomer of cetirizine or a pharmaceutically acceptable salt of any of these.

The present invention also concerns the use of a compound selected from efletirizine, cetirizine or an individual optical isomer of cetirizine or a pharmaceutically acceptable salt of any of these for the preparation of a medicament intended for preventing, or delaying the onset of, urticaria.

In accordance with the invention the selected compound is administered to the patient prior to the onset of the urticaria attack or the primary urticaria (e.g. before any biological or clinical symptoms of urticaria disease occur (primary prevention) or after biological signs of sensitization to an allergen but before the onset of symptoms of an urticaria attack (secondary prevention)).

The present invention also concerns the use of the selected compound for the preparation of a medicament intended for preventing the onset of primary urticaria in a patient, the said medicament being administered to the patient prophylactically after a resolved urticaria attack in order to prevent the re-occurrence of the disease .

It has been shown that the effect of cetirizine in urticaria is two-fold: firstly cetirizine prevents the occurrence of acute urticaria and secondly when acute urticaria occurs the patients, especially children, treated with cetirizine have fewer episodes of acute urticaria than non-treated patients.

The term "pharmaceutically acceptable salts" as used herein refers not only to addition salts with pharmaceutically acceptable non-toxic organic and inorganic acids, such as acetic, citric, maleic, succinic, ascorbic, hydrochloric, hydrobromic, sulfuric, and phosphoric acids and the like, but also to metal salts (for example sodium or potassium salts) or ammonium salts, the amine salts and the amino acid salts. Accordingly efletirizine and cetirizine may each be employed as the free acid or in the form of a pharmaceutically acceptable salt. The best results have been obtained with the dihydrochloride salt.

By patient, is to be understood adults, infants and children, in particular young children. Generally, the patients most benefiting from treatment in accordance with the invention are infants or children aged 1 week to 10 years, preferably aged 6 months to 5 years, and more preferably 10 months to 5 years. The best results have been obtained with patients aged 1 to 3.5 years.

Preferably patients treated in accordance with the invention are those not currently affected by urticaria disease and most preferably, those who have never been affected thereby.

A therapeutically effective amount of a compound selected from efletirizine, cetirizine or an individual optical isomer of cetirizine or a pharmaceutically acceptable salt of any of these is used to prevent, or delay onset of, an urticaria attack and/or primary urticaria. The dosage employed will depend essentially on the specific method of administration and on the purpose of the prophylaxis. The size of the individual doses and the administration program can best be determined based on an individual assessment of the relevant case. The methods required to determine the relevant factors are familiar to the expert.

A preferred daily dosage for use in accordance with the invention is from about 0,0005 mg to about 2 mg of the selected compound, per kg of body weight per patient. A particularly preferred daily dosage is from about 0,005 to about 2 mg per kg of body weight per patient. The best results are obtained with a daily dosage from about 0,05 to 1 mg per kg of body weight per patient, preferably 0,5 mg. The dosage may be administered once per day of treatment, or divided into smaller dosages, for examples 1 to 4 times a day, and preferably 1 to 3 times a day, and administered over about a 24 hours time period to reach a total given dosage. Best results are obtained with administration twice a day in two equal doses per day or once a day in retarded release form. The exact dosages in which the compositions are administrated can vary according to the type of use, the mode of use, the requirements of the patient, as determined by a skilled practitioner. The exact dosage for a patient may be specifically adapted by a skilled practitioner, in view of the severity of the condition, the specific formulation used, and other drugs which may be involved.

Pharmaceutical compositions used according to the present invention may be administered by any conventional means. The routes of administration include intradermal, transdermal, slow release administration, intramuscular, oral and intranasal routes, fast release, dry syrup. Any other convenient route or form of administration can be used, for example absorption through epithelial or mucocutaneous linings.

The pharmaceutical forms according to the present invention may be prepared according to conventional methods used by pharmacists. The forms can be administered together with other components or biologically active agents, pharmaceutically acceptable surfactants, excipients, carriers, diluents and vehicles.

The pharmaceutical compositions of the invention may include any conventional therapeutically inert carrier. The pharmaceutical compositions can contain inert as well as pharmacodynamically active additives. Liquid compositions can for example take the form of a sterile solution which is miscible with water. Furthermore, substances conventionally used as preserving, stabilizing, moisture-retaining, and emulsifying agents as well as substances such as salts for varying the osmotic pressure, substances for varying pH such as buffers, and other additives can also be present. If desired an antioxidant can be included in the pharmaceutical compositions. Pharmaceutical acceptable excipients or carriers for compositions include saline, buffered saline, dextrose or water. Compositions may also comprise specific stabilizing agents such as sugars, including mannose and mannitol. Carrier substances and diluents can be organic or inorganic substances, for example water, gelatine, lactose, starch, magnesium stearate, talc, gum arabic, polyalkylene glycol and the like. A prerequisite is that all adjuvants and substances used in the manufacture of the pharmaceutical compositions are nontoxic.

Pharmaceutical compositions can also be administered by spray inhalation. Any conventional pharmaceutical composition for spray inhalation administration may be used. Another preferred mode of administration is by aerosol.

The pharmaceutical composition of the invention can also be formulated for topical application. The composition for topical application can be in the form of an aqueous solution, lotion or jelly, an oily solution or suspension or a fatty or emulsion ointment.

The pharmaceutical composition of the invention can also be used for slow prolonged release with a transdermal therapeutic system in polymer matrix or with an appropriate formulation for oral slow release.

The pharmaceutical compositions according to the present invention may also be administered orally or rectally. They may also be administered by nasal instillation (aerosols) or in the form of unguents or creams. The pharmaceutical compositions

which can be used for oral administration may be solid or liquid, for example, in the form of uncoated or coated tablets, pills, dragees, gelatine capsules, solutions, syrups and the like. For administration by the rectal route, the compositions containing the compounds of the present invention are generally used in the form of suppositories.

The pharmaceutical forms, such as tablets, drops, suppositories and the like, are prepared by conventional pharmaceutical methods. The compounds of the present invention are mixed with a solid or liquid, non-toxic and pharmaceutically acceptable carrier and possibly also mixed with a dispersing agent, a disintegration agent, a stabilizing agent and the like. If appropriate, it is also possible to add preservatives, sweeteners, coloring agents and the like.

Preferably, the pharmaceutical composition of the invention is administered in traditional form for oral administration, such as film coated tablets, lozenges, dragees, and oral liquid preparation such as syrup.

Best results are obtained with an oral dosage form, in particular liquid formulations. For example, patients can receive 2 doses of 0,25 mg/kg (total daily dose : 0,50 mg/kg/day) of an oral solution of cetirizine 10 mg/ml per day; one ml of the solution contains 20 drops and one drop of cetirizine solution contains 0,5 mg.

As an example of a composition according to the present invention, the following formulation of a syrup (oral drops) is preferred: cetirizine dihydrochloride, methyl- and propylparaben, saccharinum, and purified water.

As an example of a composition according to the present invention, the following formulation of a film coated tablet is preferred: cetirizine dihydrochloride, magnesium stearate, cellulose, lactose and silicon dioxide.

Pharmaceutical compositions of the invention are useful prophylactically. These compositions can delay or prevent the onset of urticaria attack or delay or prevent the onset of urticaria itself.

The method of the invention is believed particularly suited for use in atopic patients. By atopic patient, is understood a patient predisposed to development of diseases associated with excessive IgE antibody formation.

Another advantage of the invention resides in the ability of the treatment to prevent the onset of urticaria disease, in particular in atopic children, and also in atopic children suffering from atopic dermatitis. Specifically the patients are atopic children suffering from atopic dermatitis and with a positive family history of atopy. For example, early treatment with cetirizine dihydrochloride (initiated between 1 and 2 years of age) decreased from 16 % in the placebo group to 6 % in the treated group the number of children suffering from atopic dermatitis and with a direct relative family history of atopy, who had experienced one or more urticaria episode. Another advantage of the invention resides in the ability of the treatment to prevent acute

urticaria and reduce the number of episodes per child subsequent to its urticaria initiation.

The pharmaceutical composition of the invention may be used to prevent the onset of primary urticaria in patients considered to be at high risk of developing the disease.

The invention is further defined by reference to the following example.

Example

Study on the effect of long-term treatment with the H_1-receptor antagonist cetirizine in the prevention of urticaria in young children with atopic dermatitis.

The study had a prospective, double-blind, parallel-group, placebo-controlled design, 817 children with atopic dermatitis but no asthma or other systemic disorder, who were 12-24 months old at study entry and had at least one allergic parent or sibling, were randomized. The cetirizine dose of 0.25 mg/kg twice daily, or placebo solution similar in appearance, was administered as drops with breakfast and with the evening meal every day for 18 months. After treatment with cetirizine or placebo was discontinued, the study continued in a double-blind manner for an additional 6 months.

Throughout the study, the child's primary caregiver recorded all symptoms, events and medications administered on a diary card, weekly when the child was well, and daily when the child was having symptoms. At 9 regularly scheduled visits : before treatment with cetirizine or placebo, at 1, 3, 6, 9, 12, 15, and 18 months during treatment, and at 24 months (6 months after discontinuation of the study treatment), the information recorded in the diary cards was reviewed and validated with the investigator and entered on the case record form. Before data analysis, the description of the symptom or event was transcribed verbatim from the case record forms and classified according to World Health Organization terminology. Symptoms or events with different WHO preferred terms or different dates of onset were counted as different events. A symptom or event was counted as urticaria when hives, or areas of skin swelling, redness and itching distinct from the child's atopic dermatitis, were reported. The urticaria was considered to be associated with infection if sore throat, pharyngitis, tonsillitis, "cold", upper respiratory tract infection, ear infection, vomiting, diarrhea, gastroenteritis, fever, "flu", or "virus" were reported concurrently with the hives, or within the time frame of 7 days before, or 7 days after the hives appeared.

The Frequency of children with urticaria was compared in the two treatment groups using the Fisher exact test. Use of medications in addition to study medication was compared in the two treatment groups using the x^2 test.

During the 18-month treatment phase, only 23 of the 399 children treated with cetirizine (5.8 %), had one or more urticarial episodes, in contrast to 64 of the 396

children (16.2 %) treated with placebo ($p<0.001$). Also, the children treated with cetirizine had fewer episodes of urticaria per child. During the 6-month follow-up phase, there was no difference with regard to the number of episodes of urticaria in the children previously treated with cetirizine and those previously treated with placebo.

During the 18-month treatment phase with cetirizine or placebo, the child's personal physician, while not encouraged to prescribe additional H_1 receptor antagonists, was allowed to do so if necessary. Fewer children treated with cetirizine (138 of 399, 34.6 %) received additional oral prescription or non-prescription H_1-antagonists in comparison to those treated with placebo (164 of 396, 41.4 %, $p= 0.047$).

In this study, a relatively high cetirizine dose, approximately twice that recommended world wide for use in children age 2-6 years, was administered. Despite this, cetirizine was free from adverse effects, including central nervous system and cardiovascular system effects. The rationale for twice-daily dosing was that in very young children, cetirizine has a shorter terminal elimination half life and a shorter duration of action as assessed by suppression of the histamine-induced wheal and flare in the skin than it does in older children and adults.

CLAIMS

1. The use of a compound selected from efletirizine, cetirizine or an individual optical isomer of cetirizine or a pharmaceutically acceptable salt of any of these for the preparation of a medicament intended for preventing, or delaying the onset of, an urticaria attack in a patient.
2. The use of a compound selected from efletirizine, cetirizine or an individual optical isomer of cetirizine or a pharmaceutically acceptable salt of any of these for the preparation of a medicament intended for preventing, or delaying the onset of, primary urticaria in a patient.
3. The use of a compound selected from efletirizine, cetirizine or an individual optical isomer of cetirizine or a pharmaceutically acceptable salt of any of these for the preparation of a medicament intended for preventing, or delaying the onset of, acute urticaria in a patient.
4. The use of a compound selected from efletirizine, cetirizine or an individual optical isomer of cetirizine or a pharmaceutically acceptable salt of any of these for the preparation of a medicament intended for preventing, or delaying the occurrence or re-occurrence of urticaria in a patient.
5. Use according to claim 1, 2, 3 or 4, wherein the selected compound is the cetirizine dihydrochloride.
6. Use according to claim 1, 2, 3, 4 or 5, wherein the patient is an infant or a child.
7. Use according to claim 6, wherein the patient is aged 1 to 3,5 years.
8. Use according to any one of claims 1 to 7, which comprises administering a daily dosage from about 0,0005 mg to about 2 mg of cetirizine or individual optical isomer of cetirizine or pharmaceutically acceptable salt of these, per kg of body weight per patient.
9. Use according to any one of claims 1 to 8, wherein the patient is an atopic patient.
10. Use according to claim 9, wherein the patient suffers from atopic dermatitis or has a direct family history of atopy.